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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,098	MIYAZAKI ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8 and 13-32* is/are pending in the application.

4a) Of the above claim(s) *13-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8 and 22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/16/10, 4/8/10 and 5/13/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 6, 8 and 13-32 are all the pending claims for this application.

2. Claims 1 and 28 were amended and new Claims 29-32 were added in the Response of 2/16/10.

3. Claims 13-21 are withdrawn from examination.

4. The amendments to the specification in the Response of 2/16/10 have been considered and entered.

5. Claims 1, 6, 8, and 22-32 are all the pending claims under examination.

6. This Office Action is final.

Information Disclosure Statement

7. The IDS' of 2/16/10, 4/8/10 and 5/13/10 have been considered and entered. The initialed and signed 1449 forms are attached.

Withdrawal of Rejections

Claim Rejections - 35 USC § 101

8. The rejection of Claims 1, 6, 8, 22, 23, 27 and 28 under 35 U.S.C. 101 because the generic claims 1 and 28 are drawn to a non-operative invention, namely, a eukaryotic host cell effectively expressing two different antibodies is withdrawn.

Applicants have amended independent claims 1 and 28 to specify that the eukaryotic host cell is recombinant and that the DNAs or nucleic acids encoding the heavy and light chains are exogenous.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. The rejection of Claims 1, 6, 8 and 22-32 under 35 U.S.C. 103(a) as being unpatentable over Ridgeway et al., (Protein Eng. 9:617-612 (1996); cited in the IDS of 4/28/06) in view of Peipp et al., (Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) and Shalaby et al., (J. Exp. Med. 175:217-225 (1992); cited in the IDS of 4/28/06) is maintained.

The rejection was set forth in the Office Action of 10/23/07 as follows:

"Ridgeway describes a process for producing a bispecific antibody having an Fc region, wherein the H chain and L chain which constitute a first set have a antigen recognition site and the H chain and L chain which constitute a second pair have another antigen recognition site and are expressed simultaneously, and the formation of the first pair and the second pair and the bonding of said first pair and second pair by knobs-in-hole are carried out simultaneously. Ridgeway also describe antibodies produced having antigen recognition sites comprising the H chain which makes up the first pair and the L chain which makes up the second pair. Ridgeway does not disclose expressing the first and second antibodies at different times but Peipp and Shalaby rectify this deficiency.

Peipp and Shalaby are discussed supra.

One skilled in the art would have been motivated at the time of the invention to have made the process for producing a bispecific antibody having an Fc region and been reasonably assured of success based on the disclosures of Ridgeway, Peipp and Shalaby. The method of Ridgeway could readily have been modified by one of skill in the art based on Pipp and Shalaby disclosing that the separate expression of an H chain and L chain which constitute a first pair having a particular antigen recognition site and an H chain and L chain which constitute a second pair having another antigen recognition site, and to bond their respective H chain and L chains in advance, forming a first pair and a second pair having antigen recognition site, and subsequently bonding the first pair and second pair via knob-in-hole, in order to prevent the production of antibodies having antigen recognition sites comprising undesirable sets and to efficiently produce the target bispecific antibody. Further one of skill in the art could introduce an optimum expression regulating factor and carry out the expression of the H chain and L chain which constitute the first pair, and an H chain and L chain which constitute the second pair in separate cells at

different times. Because Ridgeway taught the general method for producing bispecific antibodies and Peipp and Shalaby describe different techniques for expressing different antibody pairs from different vectors could be accomplished in E. coli, one of ordinary skill in the art could have readily introduced the vector system of Peipp or Shalaby into the method of Ridgeway and would be reasonably assured that the expressed antibody pairs would have formed a bispecific antibody."

The rejection was maintained in the Office Action of 9/11/08 as follows:

"Applicants' allegations on p. 11 of the Response of 4/23/08 have been considered but are not found persuasive. Applicants allege "Indeed, the knobs-in-holes method used by Ridgeway is very similar to that of Carter"; and the rejection over Ridgeway, Peipp and Shalaby is incorrect for the same reasons the rejection over Carter, Peipp and Shalaby is incorrect.

Response to Arguments

Applicants do not appear to have taken the time to review Ridgeway, or the disclosure relied on by the examiner was overlooked. Ridgeway teaches co-transfection of phagemids encoding the anti-CDR3 L chain and H chain into human embryonic kidney cells, 293S, *together* with a CD4IgG variant encoding phagemid. This is interpreted as the antibody being expressed by the same cell. Mutations were constructed in the CH3 domain of humanized anti-CD3 Ab H chain and in the CD4-IgG, and the CH3/CH3 interface involves 16 residues on each domain. In contrast to chains containing the wild-type CH3, the hybrid was recovered in yields of up to 92% from co-transfections in which the anti-CD3 H chain and CD4-IgG contained the Y407T hole and T366Y knob mutations, respectively. Further because each of the Ab and the CD4-IgG of Ridgeway is expressed on a different phagemid within the same cell, there is no requirement that the proteins would necessarily be expressed at the same time absent a showing by Applicants to the contrary.

Ridgeway states: "This augurs well for the preparation of larger quantities of hybrids using stable cell lines where the relative expression levels of the Ab and CD4-IgG are less readily manipulated than in the transient expression system used here."

Ridgeway states: "The T366Y and Y407T mutations are directly applicable to the construction of bispecific IA, which further expand IA as a class of novel therapeutic. In addition the mutations identified are anticipated to increase the clinical potential of ***Fc-containing BsAb*** by reducing the complexity of the mixture of products obtained from a possible 10 major species down to four or less."

Rideway provides sufficient motivation to use the holes-to-knobs approach in a single cell system to create other antibody fragments such as the bispecific antibodies of the instant claims including the BsF(ab)2 of Shalaby. Shalaby provides methods for expressing a Fab' in a dicistronic format where both the light chain and heavy chain are under the transcriptional control of the phoA promoter. The general skills and technology to modify the expression unit of Ridgway according to the expression units of Shalaby for use in the method of Ridgeway would seemingly have been obvious at the time of the invention especially to produce a full length bispecific antibody within the same cell.

Rideway provides sufficient motivation to use the holes-to-knobs approach in a single cell system to create other antibody fragments such as the bispecific antibodies of Peipp. Peipp teaches "Recombinant bispecific antibodies can be successfully produced in various expression systems (see Table 2 for examples of expressing recombinant bispecific antibodies in CHO cells)"...and "While bacterial expression offers the potential for large yields, difficult refolding procedures may be required to obtain functional proteins. Today, production in Escherichia coli is most commonly used for the diabody format, while short-chain bispecific antibodies are preferentially expressed in mammalian cells. Interesting novel expression systems include yeast or insect cells, as well as transgenic plants or animals [38,39]. For production of clinical-grade material, however, these later systems are less well defined regarding potentially dangerous contaminants, and furthermore differ substantially from mammalian cells with respect to their glycosylation pattern."

Thus in order to produce abundant yield of heterodimeric, bispecific antibodies which are optimally expressed, dimerize with their corresponding complementary chain and are properly glycosylated, the ordinary artisan would have found more than sufficient motivation to have used the method of Ridgeway as a starting point for expressing heterodimeric antibodies in a single eukaryotic cell using a dicistronic vector or separate vectors encoding the light and heavy chain complementary pairs in order to ensure differentially timed expression for equimolar expression and dimerization of the complementary light and heavy chain in order to avoid mispairing followed by the further pairwise association of the different heavy chains through the knobs-to-holes variation.

The rejection was maintained in the Office Action of 8/13/09 as follows:

"Applicants' allegations on pp. 7-9 of the Response of 6/10/09 have been considered and are not found persuasive. Applicants allege that none of the references teach "anything about controlling the timing of expression of heavy and light chains within a cell" and "the use of four different chains: two light chains and two heavy chains"; and "the references teach that, in order to ensure proper pairing of heavy and light chains in a bispecific antibody context, one should either (a) express one pair in one set of cells and the other pair in a different set of cells, or (b) reconfigure them as recombinant diabodies or single-chain bispecific antibodies."

Response to Arguments

The examiner respectfully submits that the references are not so limited as to the possibility of resultant antibodies that could be generated from combining their disclosed techniques. For example, and as stated in the Office Action of 9/11/08, Shalaby provides methods for expressing a Fab' in a dicistronic format where both the light chain and heavy chain are under the transcriptional control of the phoA promoter. The general skills and technology to modify the expression unit of Ridgway according to the expression units of Peipp and Shalaby for use in the method of Ridgeway would seemingly have been obvious at the time of the invention especially to produce a full length bispecific antibody within the same cell. For example Peipp provides in Figure 1 (3rd example, top row), "Schematic representation of the most common bispecific antibody formats" and specifically shows an example of a knobs-into-holes antibody comprising two different light chains and two different heavy chains where the heavy chains are linked by the knobs-into-holes feature engineered into the constant region of the heavy chain. Finally, as stated in the Office Action of 9/11/08, Ridgeway states on p. 620, Col. 2, ¶4: "The T366Y and Y407T mutations are directly applicable to the construction of bispecific IA, which further expand IA as a class of novel therapeutic. In addition the mutations identified are anticipated to increase the clinical potential of Fc-containing BsAb by reducing the complexity of the mixture of products obtained from a possible 10 major species down to four or less. The T366Y and Y407T mutant pair will likely be useful for heterodimerization of other human IgG isotypes since T366 and Y407 are fully conserved and other residues at the CH3 domain interface of IgG1 are highly conserved." Ridgeway specifically contemplates that the knobs-to-holes technique could be expanded to include other full length IgG molecules. Further and as evidenced by the references alone or in combination and the general state of art at the time of the invention, cloning the two different heavy chain and two different light chains to read on the vector constructs of Claims 24-26 would have been well within the skill of the ordinary artisan for recombinant antibody technology. (MPEP 2141; *KSR* stating a rationale for obviousness includes an "obvious to try" where the ordinary artisan would choose from a finite number of identified, predictable solutions, with a reasonable expectation of success"). Here both Ridgeway and Shalaby were successful in using different techniques to co-express two light chain and two heavy chains and thus to have combined the techniques further in view of Piepp who illustrated the resultant claimed antibody product with knoeb-to-holes would have been prima facie obvious at the time of the invention. Additionally, that the ordinary artisan would use an expression-inducible promoter such as tetracycline was well known in molecule biology and availabel to the ordinary artisan.

The obviosness of using knobs-to-holes is admitted by Applicants' own attorney statements of record, where on p. 11 of the Response of 6/10/09, they state: That this technique is well known in the art is illustrated by the fact that at least three publications of record (Ridgway, Peipp and the previously-cited Carter, J. Immunol. Methods 248:7-15, 2001) describe its use in production of bispecific antibodies. Knowledge of the technique thus goes back to at least 1996."

Applicants allegations on pp. 8-13 of the Response of 2/16/10 have been considered and are found persuasive.

a) Applicants allege "Ridgway was able to create heterodimers by the "knobs-into-holes" engineering design strategy, and predicted that this technique, if applied to bispecific antibodies, would reduce the number of random mispairings that occur in the

cell from "10 major species down to four or less." Ridgway's reference to "four or less" species reflects his recognition that the problem of mispairing of a light chain with the incorrect heavy chain is not solved by the knobs- into-holes technique. Ridgway simply avoided this problem in his own experiments by using only one kind of light chain and one kind of heavy chain, and having the CD4 IgG fusion polypeptide serve as the second arm."

Response to Arguments

Initially, the examiner submits that Applicants conjecture about what Ridgeway was contemplating by using only one kind of light chain and one kind of heavy chain is unsubstantiated by extrinsic evidence. Applicants do not identify support in Ridgeway for this allegation.

Secondly, Applicants fail to recognize that Ridgeway appreciates using the knobs-into-holes techniques for pairing bi-specific Fc-containing antibodies when the range limitation "four *or less*" reads on no mispairings. In other words, Ridgeway recognizes the existence of experimental error along with the possibility of achieving fully matched antibody pairings with no error. Ridgeway teaches and provides motivation to use knobs-in-holes for bi-specific antibody pairing on p. 620, Col. 2, ¶4:

> "The T366Y and Y407T mutant pair will likely be useful for heterodimerization of *other human IgG isotypes* since T366 and Y407 are fully conserved and other residues at the CH3 domain interface of IgG1 (Deisenhofer, 1981; Miller, 1990) are highly conserved (Kabat et al., 1991)."

Thirdly, Ridgeway provides at the very least a scintilla of evidence needed to establish prima facie motivation to try using the knobs-into-holes technique in the same cell expressing different Fc-containing antibodies. It is the examiner's position that it would have been obvious to try using the knobs-into holes technique for making bispecific antibodies in the same cell where as in the present case the ordinary artisan would have chosen "from a finite number of identified, predictable solutions, with a reasonable expectation of success" (*KSR*, 550 U.S. at ___, "2 USPQ2d at 1396).

b) Applicants allege "rather than teaching a temporally separated expression of the two arms in order to control proper pairing of light and heavy chains, the approaches taught in the cited art to overcome the mispairing of the light and heavy chains include: (1) using a single, Fc-containing fusion polypeptide (CD4-IgG) as the second arm instead of using a heavy chain associated with a light chain as the second arm (Ridgway); (2) expressing the antigen binding fragments (Fab') of two different antibodies in separate cells and chemically coupling the purified Fab' fragments to form a heterodimer (Shalaby); and (3) using identical light chains (Peipp/Carter)."

Response to Arguments

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a temporally separated expression of the two arms in order to control proper pairing of light and heavy chains) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed.

Cir. 1993). Here the claims merely recite that cessation of the expression of the first antibody is overlapping with inducing expression of the second antibody. There is no clear division or distinction between steps c) and d) of Claims 1 and 28 where expression of the first antibody is fully inhibited before induction of the second antibody.

The rejection is maintained.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

10. The rejection of Claims 1, 6, 8, and 22-32 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for inducing just any kind of recombinant cell to express a first light chain and a first heavy chain at one time and then to express a second light chain and a second heavy chain *at a different time under just any conditions*.

For purposes of review, the rejection was set forth in the Office Action of 9/11/08 as follows:

> "Nature of the Invention/ Skill in the Art
> Claims 1, 6, 8 and 22 are interpreted as being drawn to a method for producing an antibody in a cell comprising expressing a first light and heavy chain at one time and expressing a second light and heavy chain at a different time and where the light chains are different and the heavy chains are different (Claim 1), where the antibody is bispecific and the first light and heavy chain recognize one antigen and the second light and heavy chain recognize a second antigen (Claim 6), where the antibody is prepared by using the knobs-into-holes technique (Claim 8), and where the first light and heavy chain expression is under the control of a first expression regulator and the second light and heavy chain expression is under the control of a second expression regulator and each of the expression regulators are different, where (i) the first light and heavy chain and second light and heavy chain are encoded by the

same vector or (ii) the first light and heavy chain are encoded by a first vector and the second light and heavy chain are encoded by a second vector (Claim 22).

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure of the Specification

Specific examples of methods for expressing the first and second pairs of antibodies at different times include methods that induce the expression of the first and second pairs of antibodies at different times using expression regulators. More specifically, a vector in which expression of a first pair can be induced by a first expression regulator, and a vector in which expression of a second pair is inducible by a second expression regulator, are constructed. The first pair and second pair may be constructed in a single vector, or two or more different vectors. Alternatively, the H chain and L chain may be constructed in a single vector, or two or more different vectors. Next, the obtained vector constructs are introduced into cells, and expression of the first pair is induced by the first expression regulator, and then expression of the second pair is induced by the second expression regulator. In this case, expression of the first pair is preferably turned off before expression of the second pair is induced [0056].

A specific example of the methods for producing antibodies of the present invention is described where "First, the H and L chains on the left arm of an antibody (Left HL) and the H and L chains on the right arm of the antibody (Right HL) are respectively cloned into a tetracycline inducible pcDNA4 vector (Invitrogen) and an ecdysone inducible pIND vector (Invitrogen). All of the expression-regulated plasmids are introduced into the above-mentioned suitable host cells, for example, animal cells such as COS-7 cells. For example, for the first induction tetracycline is added to the medium, and a Left HL molecule is formed in the cells. One to two days after the first induction, the medium is washed away to completely remove the first agent (tetracycline, in this case). Next, the cells are placed in a fresh medium containing an ecdysone analogue, the agent for the second induction, and the second induction is conducted for two to three days. Consequently, a Right HL molecule is produced and associates with the Left HL molecule already present in the cells, thus forming a complete BsAb form, which is then secreted into the medium" [0065].

The expression regulators are not particularly limited, and any kinds of expression regulators may be used as long as they can regulate expression of H chains and L chains in host cells. For example, expression may be induced in the presence of an expression regulator, and not in its absence; or conversely, expression may be induced in the presence of an expression regulator, and not in its absence. Expression regulators may be chemical compounds such as expression inducing agents, or physical factors such as temperature (heat). Specific examples of expression inducing agents include antibiotics such as tetracycline, hormones such as ecdysone analogues, and enzymes such as Cre (a homologous recombination enzyme which causes recombination). In addition, induced expression of an H chain and/or L chain may be halted by removing the expression inducing agent that functions as an above-mentioned expression regulator. If a physical factor such as temperature (heat) is used as an expression regulator, the induced expression of an H chain and/or L chain can be halted by returning to a temperature that does not permit induction of expression [0057].

Claim 22, element (i) is drawn to expressing both antibody pairs from the same vector, and the specification provides a single statement for expressing both antibody pairs from the same vector. No examples of a poly-cistronic expression vector are taught or disclosed, and no references citing examples of a poly-cistronic expression vector are cited which meet all the required claim limitations.

A method using any cell with the properties of the instant claims is unpredictable and requires undue experimentation.

In order to obtain a bispecific antibody comprising the heavy and light chain constant domains and using the knobs-to-holes technique required by the instant method, and in order to produce abundant yield of heterodimeric, bispecific antibodies which are optimally expressed and dimerize with their corresponding complementary chain and are properly glycosylated, the ordinary artisan could not have used just any wild-type cell as instantly claimed. This is because according to Peipp (Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) "Recombinant bispecific antibodies can be successfully produced in various expression systems (see Table 2 for examples of expressing recombinant bispecific antibodies in CHO cells)"...and "While bacterial expression offers the potential for large yields, difficult refolding procedures may be required to obtain functional proteins. Today, production in Escherichia coli is most commonly used for the diabody format, while short-chain bispecific antibodies are preferentially expressed in mammalian cells. Interesting novel expression systems include yeast or insect cells, as well as transgenic plants or animals [38,39]. For production of clinical-grade material, however, these later systems are less well defined regarding potentially dangerous contaminants, and furthermore differ substantially from mammalian cells with respect to their glycosylation pattern." Further, Ridgeway et al., (Protein Eng. 9:617-612 (1996); cited in the IDS of 4/28/06) teach the successful use of an in vitro eukaryotic cell system to express an Ab/CD4-IgG using the knobs-to-holes technique which is taught as being adaptable to creating bispecific antibodies.

The specification does not nearly suggest that the ordinary artisan could remotely practice the invention using any cell and in the absence any particular reagents as is otherwise required by the instant claims. The ordinary artisan would be required to practice undue trial and error experimentation just to identify any wild-type cell having the

ability to differentially express a first light and heavy chain much less a second light and heavy chain within the same cell, and further wherein the antibody is generated using a knobs-into-holes technique when the instant claims which do not specify where within the antibody structure, the knobs-to-holes mutation should be introduced. Thus Applicants have not identified a naturally occurring cell that can be induced under any conditions to express two different antibodies (or antibodies against different antigens) within or by the same cell.

Similarly, the ordinary artisan would be required to perform undue trial and error experimentation to test various different compounds for expression regulating effects on the endogenous promoters for the first light and heavy chain, and different compounds for expression regulating effects on the endogenous promoters for the second light and heavy chain, especially where the compound-inducible expression regulation is required to be performed in the same cell in order for the same wild-type cell to differentially express the different light/heavy chain pairs.

The ordinary artisan would be required to practice undue trial and error experimentation in order to construct a poly-cistronic vector enabled to express in a different time frame the first antibody pair and then the second antibody pair and all occurring within the same cell, because no guidance is provided in the original specification as filed for the starting materials and/or the generation of any such vector construct.

Applicants could overcome the rejection by introducing amendments into the method claims more particularly describing those steps and reagents which are required to practice the method as supported and enabled by the original disclosure."

The rejection was maintained in the Office Action of 8/13/09 as follows:

"Applicants' allegations on pp. 10-12 have been considered and are not found persuasive. Applicants allege "one of ordinary skill in the art would presumably seek a simple route to the final result: e.g., transfecting the cell with recombinant nucleic acid encoding the four polypeptides, with expression of the mRNAs encoding the polypeptides driven by known inducible promoters" and that the instant claims read on such elements. For example, "In the methods of the invention, the four polypeptides could be encoded on two separate bicistronic vectors, as illustrated in Example 1 of the specification. Alternatively, the four polypeptides could be encoded on four separate vectors (one coding sequence per vector) or on three vectors (two coding sequences on one, and one coding sequence on each of the other two), or all on a single vector. (The vectors could, of course, be integrated into the cell's genome to produce a stably transfected cell.)"; and "That this technique *[knobs-into-holes; examiner's italics]* is well known in the art is illustrated by the fact that at least three publications of record (Ridgway, Peipp and the previously-cited Carter, J. Immunol. Methods 248:7-15, 2001) describe its use in production of bispecific antibodies. Knowledge of the technique thus goes back to at least 1996."

Response to Arguments

The examiner respectfully submits that the amendment of the claims to read on a eukaryotic cell does not obviate the original grounds for rejection, which is that Applicants have yet to demonstrate a working example of a wild-type eukaryotic cell capable of being used in the invention method to co-express two light chains and two heavy chains where the heavy chains are paired via knobs-to-holes. Thus absent Applicants submission of evidence showing any such cell exists much that it is capable of undergoing these steps or amending the generic claims 1 and 28 to indicate that the eukaryotic cell is *recombinant and vector transformed*, the skilled artisan could not conceivably practice the invention without further and undue experimentation. This rejection is maintained because the claims fail to meet the how-to-use aspect of the
enablement requirement."

Applicants allege that in amending independent claims 1 and 28 to recite, in relevant part, that the eukaryotic cell is recombinant and that the DNAs or nucleic acids encoding the heavy and light chains are exogenous, overcomes the rejection.

Response to Arguments

The examiner's review of Applicants comments in the Response of 2/16/10 in general are revealing insofar as what Applicants emphasize as being critical elements of the method. It is understood that the cell must be recombinant for two different antibodies in order for the invention to be operative. However, Applicants admissions of record point to other critical elements required for achieving the differential temporal expression pattern of the first and second antibodies. Applicants admit that expression of the first antibody chains must be stopped and then the chain products are allowed to fold in order to avoid mispairing with the second expressed antibody chain products. For example, under the 103(a) rejection, Applicants emphasize on p. 9 of the Response:

> "In sum, temporal expression of the chains of the first and second arms solves the problem of random mispairing of the two heavy and two light chains of the bispecific antibody into10 different arrangements."

The specification in Example 2 teaches temporal differential expression of bispecific antibodies requires "a mixture of six kinds of plasmid DNA, comprising pcDNA1-24H, pcDNA1-24L, pIND2-7H, pIND2-7L, pcDNA6/TR, and pVgRXR for transfeetion into animal cells." And in order to get this mixture to work, the ordinary artisan must add tetracycline to express the first antibody followed by adding an analogue of the insect hormone ecdysone.

The specification in Example 4 teaches "One antibody sample was expressed by simultaneous induction with tetracycline and ponasterone A after transfection (simultaneous induction), and the other was expressed by induction with tetracycline for one day followed by induction with ponasterone A for two days (temporal differential expression).... the samples in which expression of each HL molecule was induced at

different times showed about a twofold higher binding ability per unit antibody level than samples in which both HL molecules were expressed simultaneously."

Thus in order to obtain two different functional antibodies being expressed in and by the very same eukaryotic cell, it is not sufficient to perform step c) in Claims 1 and 28 (where the expression of the first antibody chains are ceased) before performing step d) (where the expression of the second antibody chains are induced). For the generic method to meet the enablement requirement, expression of the second antibody must be under the control of different inducing elements that are separate and distinct from the inducing elements used for inducing expression of the first antibody. Applicants would have the Office believe that the generic method is easily practiced and therefore enabled by merely following the broad and generic steps of Claims 1 and 28, however, MPEP 2138.05 citing *Birmingham v. Randall*, 171 F.2d 957, 80 USPQ 371, 372 (CCPA 1948) states: "To establish an actual reduction to practice of an invention directed to a method of making a product, it is not enough to show that the method was performed. "[S]uch an invention is not reduced to practice until it is established that the product made by the process is satisfactory, and [ ] this may require successful testing of the product."

The ordinary artisan would be required to practice undue trial and error experimentation just to identify any recombinant cell having the ability to differentially express a first light and heavy chain much less a second light and heavy chain within the same cell, and further wherein the antibody is generated using a knobs-into-holes technique (Claim 8) when the instant claims which do not specify where within the

antibody structure, the knobs-to-holes mutation should be introduced much less where the first and/or second heavy chains contain mutations the promote formation of multimers (Claim 23). Thus Applicants have not identified a recombinant cell that can be induced under any conditions to express two different antibodies (or antibodies against different antigens) within or by the same cell.

Similarly, the ordinary artisan would be required to perform undue trial and error experimentation to test various different compounds for expression regulating effects on the endogenous promoters for the first light and heavy chain, and different compounds for expression regulating effects on the endogenous promoters for the second light and heavy chain, especially where the compound-inducible expression regulation is required to be performed in the same cell to differentially express the different light/heavy chain pairs.

The ordinary artisan would be required to practice undue trial and error experimentation in order to construct a poly-cistronic vector enabled to express in a different time frame the first antibody pair and then the second antibody pair and all occurring within the same cell, because no guidance is provided in the original specification as filed for the starting materials and/or the generation of any such vector construct.

The rejection is maintained because Applicants have not met their burden in responding to the grounds for rejection.

Conclusion

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643